November 15, 2002

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Dockets Management Branch
(HFA-305), Room 1061
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

RE: Citizen's Petition – Expansion of Bioequivalence Acceptance Criteria for Approval of Generic Animal Drugs.

To Whom It May Concern:

The undersigned submits this petition under 21 CFR 10.30 as promulgated under the Federal Food, Drug, and Cosmetic Act for which authority has been delegated to the Commissioner of Food and Drugs (under 21 CFR, Part 5.10). The petitioner requests revision of the Center for Veterinary Medicine's bioequivalence guidelines.

ACTION REQUESTED:

The petitioner requests that the Center for Veterinary Medicine's 1996 *Bioequivalence Guidance* and its subsequent versions dated July 2000, October 2000 and October 2002 be revised so that it is harmonized with the European Union's guidance, *Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products*[1](Attachment 1). This revision would specifically allow for consideration of bioequivalence for a generic product if, based on logarithmically transformed data, the 90% confidence intervals about the mean calculated for C_{max} are entirely contained within the limits of 70% to143% (or 70% to 130% for untransformed data) in situations with complex absorption kinetics, situations where the reference product has a highly variable C_{max} or where, based on clinical evidence, C_{max} has little therapeutic or toxic implication. This would also allow for consideration of bioequivalence for a generic product if, based on logarithmically transformed data, the 90% confidence intervals about the mean calculated for AUC exceed the limits of 80% to125% (or 80% to 120% for untransformed data) in situations where the compound has a large safety margin or a large efficacy window.

STATEMENT OF GROUNDS:

C_{max} is highly variable due to several factors of which the selection of sampling times and the extent of the therapeutic window are key. If the test product is more variable than the reference product, the probability of bioequivalence failure is much greater even though no clinical manifestation of difference in therapeutic response may exist. There are cases where the reference product tested against itself may not meet U.S. bioequivalency guidelines[2]. The occurrence of this anomaly questions the validity of the C_{max} bioequivalence guidelines if an existing marketed pioneer product cannot be shown to be equivalent to itself within the existing guidelines.

As stated by Martinez, et al.[2] (Attachment 2), "Clearly, large differences between treatment means or a more variable test than reference formulation could seriously impair product switchability. However, if a high level of variability is observed with both products, or if the test product has substantially less variability than does the reference, average bioequivalence methods fail to adequately identify products that will produce the same therapeutic effects." The vulnerability of the

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average bioequivalence criteria for highly variable products is implicitly acknowledged in the 2001 US FDA-CDER Guidance for Industry, *Statistical Approaches to Establishing Bioequivalence*[3] (Attachment 3) where specific alternatives for this average bioequivalence test are allowed for human products when reference product variance is large.

Consideration of the expanded acceptance limits will harmonize the U.S. guidelines with the European Agency for the Evaluation of Medicinal Products (EMEA) – *Veterinary Medicine and Information Technology* guidance established by the Committee for Veterinary Medicinal Products "Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products" Effective July 11, 2001[1]. This guidance states under the "Criteria for bioequivalence determination (bioequivalence interval)" section the following:

> "For AUC, the general rule is that 90% confidence interval for the ratio of the two treatment means should be entirely contained within the limits (80 - 125%). However, for compounds with a large safety margin or a large efficacy window, differences exceeding the limits can be tolerated. On the other hand, for compounds with steep dose-response curves, a 20% difference may be acceptable."
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> "For C_{max}, the generally acceptable limits for the 90% Confidence interval are 80% to 125%. However, as the parameter may exhibit a greater variation and is strongly dependent on the sampling scheme, limits of 70% to 143% could be acceptable, when based on clinical evidence and when pre-specified in the protocol."

The criteria requested for C_{max} would also be applicable in situations with complex absorption kinetics or where C_{max} has little therapeutic or toxic implication[2]. Modifying the acceptable boundaries for C_{max} and AUC bioequivalence is consistent with CVM's intention of harmonization of international regulatory guidelines for animal health products.

This present Citizen's Petition formalizes the option presented on page 22 of the 2002 revision of CVM's *Bioequivalence Guidance* that allows sponsors to "request for alternative bounds for the confidence interval." This petition places a reasonable limit on the boundaries of an acceptable confidence interval that would also be consistent with EU guidelines.

Therefore, the petitioner requests that current FDA-CVM bioequivalence guidance be harmonized with the EU bioequivalence guidance. This would allow for expanded confidence interval limits, as in Europe, to be formalized by inclusion in the FDA-CVM guideline criteria for establishing bioequivalence for products as defined in the Action Requested section of this petition. This request is based on rationale provided by an expert panel of FDA-CDER personnel, the American Academy of Veterinary Pharmacology & Therapeutics and the EMEA bioequivalence guidance.

ENVIRONMENTAL IMPACT:

The action of submitting this Citizen's Petition and its review by the FDA - Center for Veterinary Medicine is not expected to have an environmental impact. The action requested qualifies for categorical exclusion under 21 CFR Part 25.30(h) from the requirement for an environmental assessment and, to the best of the sponsor's knowledge, no extraordinary circumstances exist.

ECONOMIC IMPACT:

An "Economic Impact" analysis of this action will be provided if requested by the Commissioner.

CERTIFICATION:

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Citizen's Petition contains all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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References

[1] EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS – *VETERINARY MEDICINE AND INFORMATION TECHNOLOGY* GUIDANCE ESTABLISHED BY THE COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS "GUIDELINES FOR THE CONDUCT OF BIOEQUIVALENCE STUDIES FOR VETERINARY MEDICINAL PRODUCTS", EMEA/CVMP/016/00-CORR-FINAL, EFFECTIVE JULY 11, 2001.

[2] MARTINEZ, M., ET. AL., "CHALLENGES ASSOCIATED WITH THE EVALUATION OF VETERINARY PRODUCT BIOEQUIVALENCE: AN AAVPT PERSPECTIVE", J. VET. PHARMACOL. THERAP., 25, PP 201-220, 2002.

[3] U.S. DEPT. OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION (CDER), GUIDANCE FOR INDUSTRY, *STATISTICAL APPROACHES TO ESTABLISHING BIOEQUIVALENCE*, JANUARY 2001.